CORRESPONDENCE

Because we receive many more letters than we have room to publish we may shorten those that we do publish to allow readers as wide a selection as possible. In particular, when we receive several letters on the same topic we reserve the right to abridge individual letters. Our usual policy is to reserve our correspondence columns for letters commenting on issues discussed recently (within six weeks) in the BMJ.

Letters critical of a paper may be sent to the authors of the paper so that their reply may appear in the same issue. We may also forward letters that we decide not to publish to the authors of the paper on which they comment.

Letters should not exceed 400 words and should be typed double spaced and signed by all authors, who should include their main degree.

Hypoalbuminaemic hyponatraemia: a new syndrome?

SIR,—The article by Dr P Dandona and others is certainly debatable (2 November, p 1253). They describe six patients with hyponatraemia—three in some detail—and conclude that the association with hypoalbuminaemia is new. However, it is difficult to decide exactly what is new.

Is the association of hyponatraemia and hypoalbuminaemia new? This combination is normally associated with clinically detectable oedema and is well described[1]; the physiological explanation is available and quoted in the article. If the suggestion is that certain patients with hypoalbuminaemia, but without oedema, develop hyponatraemia through an unknown mechanism care should be taken to exclude patients with other potential non-osmotic stimuli to antidiuretic hormone. All three detailed cases have an additional explanation for non-osmotic stimulation.

Is the association of hypoalbuminaemia, hyponatraemia, and cerebral symptoms, corrected by restoration of plasma sodium, new? In two of the detailed cases (cases 1 and 2) hyponatraemia was not a feature until after admission, suggesting iatrogenic induction by inadequate monitoring of fluid balance. Subsequent symptoms of confusion are then perhaps not surprising if induction of the hypo-osmolal state was rapid.[2]

Is the response of plasma sodium to albumin infusion new? The restoration of normal plasma sodium has previously been observed in patients with the nephrotic syndrome.[3] It is only a palliative treatment if steps are not taken first to reverse the underlying physiological cause of water retention.

The association between hypoalbuminaemia and hyponatraemia through inspection of laboratory records is tenuous. While suggesting the association should be evaluated critically, the authors ignore their own advice. There is no more value in causally associating hyponatraemia with hypoalbuminaemia than say hyponatraemia with a raised erythrocyte sedimentation rate.

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1 Anderson RJ, Chung H-M, Kluge R, Schrier RW. Hyponatremia: A prospective analysis of its epidemiology and the pathogenic role of vasopressin. *Ann Intern Med* 1985;**102**: 164-8.
2 Arieff AI, Llach F, Massry SG. Neurological manifestations and morbidity of hyponatremia: correlation with brain water and electrolytes. *Medicine* 1976;55:121-9.
3 Davison AM, Lambie AT, Verth AH, Cash JD. Salt-poor human albumin in management of nephrotic syndrome. *Br Med J* 1974;i:481-4.

SIR,—The syndrome described by Dr P Dandona and others is identical with that complicating parenteral nutrition and leading to excessive tissue oedema and multiple organ failures.[1] Any of their cases would also meet the criteria for the transurethral resection syndrome, and their syndrome is also little different from the "Pitressin and glucose" syndrome known in obstetrics. Any of these syndromes may present as shock lung, brain oedema, or heart, renal, or hepatic failure. Detecting a change in osmolality requires careful timing before endogenous osmolar "adaptation" takes place. Although some of these patients, and those of the authors, are described as "hypovolaemic," they are not fluid depleted. The increase in weight in such patients, due to fluid retention, may be up to 4-7 kg.[1-3]

Another version of the syndrome, in which hypoproteinaemia may be associated with normal sodium and osmolality, is that which occurs as a result of excessive saline infusion. Such infusion may be inappropriately given during surgery to correct hypotension that may or may not be caused by blood or fluid loss. This syndrome may present as shock lung or diffuse capillary bleeding occurring during or soon after surgery. In spite of massive fluid overload, the central venous pressure may drop and remain low after a transient rise.[3]

This is a point that is hard to sell: hypervolaemia may lead later to hypovolaemia, hypoalbuminaemia, and a low central venous pressure because of the escape of plasma into the interstitial space. It is a well documented response to saline loading in animals,[4] as well as volume overload in humans.[1-3] The development of diuresis, natriuresis, hyponatraemia, hypervolaemia, hypovolaemia, and hypo-osmolality depends not only on the type of fluid infused but also on the ability of the heart and kidneys to handle such massive fluid overload.

The high level of antidiuretic hormone may occur earlier due to pain, infection, drugs, or anaesthesia, and as a response to the early hypovolaemia. This is a syndrome of the "oedematous hypovolaemic hypo-osmotic" patient. Its true pathology is due to alterations of the cellular and the capillary membranes, and the best management is prevention. Before discussing further pathogenesis or management of such syndromes let us straighten up some physiological issues such as Starling's law and osmolality. This may transfer the management of these syndromes from a "hit and miss" situation into a scientifically well understood medicine.

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1 Watters DAK, Chamroonkul S, Griffith CDM, *et al.* Changes in liver function tests associated with parenteral nutrition. *J R Coll Surg Edin* 1984;**29**:339-44.

2 Rhymer JC, Bell TJ, Perry KC, Ward JP. Hyponatraemia following transurethral resection of the prostate. *Br J Urol* 1985;57:450-2.
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SIR,—Dr P Dandona and his colleagues (2 November, p 1253) describe "hypoalbuminaemic hyponatraemia" and suggest that this is a new syndrome. They say that intravascular volume depletion secondary to hypoalbuminaemia may lead to hyponatraemia. This is not a new observation; it was clearly described in my undergraduate textbook of clinical chemistry.[1] The mechanism whereby hyponatraemia occurs is not clearly understood. If intravascular volume depletion results in appropriately increased secretion of antidiuretic hormone and aldosterone and the kidney can respond appropriately hyponatraemia should not occur.

To ascribe hyponatraemia in the cases described solely to the action of antidiuretic hormone on the basis of urine and plasma osmolalities alone is unjustified. I would like to see a study in which measurements include central venous pressure, urinary electrolytes, plasma and urinary osmolalities, and plasma concentrations of antidiuretic hormone, aldosterone, and atrial natiuretic peptide. A control group of hypoalbuminaemic but non-hyponatraemic patients would be desirable. Without such data one might speculate that the hyponatraemia was due to a failure of aldosterone production or that the rise in antidiuretic hormone secretion was of an inappropriate magnitude.

The cases described contained insufficient data to prove the authors' hypothesis. Intravascular volume depletion is shown only in case 3; we are not told the height of the jugular venous pressure, postural drop in blood pressure, or central venous pressure in the other cases. In case 3 why are the hyponatraemia and increased urinary osmolality not due to diuretic therapy?

Thus the authors do not describe a new cause of hyponatraemia. They may, however, be correct in suggesting that the clinical consequences of hyponatraemia in this setting are more important than previously thought and in emphasising that the correct management is to replenish intravascular volume. The physiological background needs to be investigated more carefully.

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1 Zilva JF, Pannall PR. *Clinical chemistry in diagnosis and treatment*. London: Lloyd-Zuke, 1975:53-6.

SIR,—Dr P Dandona and colleagues (2 November, p 1253) have produced evidence for a direct causal link between hypoalbuminaemia and hyponatraemia. The association was thought to be mediated by antidiuretic hormone (ADH) secreted as a consequence of hypovolaemia, which is a result of failure to maintain water in the vascular space due to reduction of the plasma oncotic pressure, to which albumin is the major contributor.

They drew an analogy with the syndrome of inappropriate secretion of ADH in that their patients presented with serum hypo-osmolality and urine hyperosmolality. These two features in isolation do not allow such an analogy because they usually occur in patients who are hyponatraemic due to saline depletion, which is often accompanied by hypovolaemia, baroreceptor stimulation, appropriate ADH secretion, and production of a hyperosmolal urine. A clear distinction needs to be made between appropriate and inappropriate ADH secretion, and for diagnosing the latter the other features of the syndrome—normovolaemia, normal adrenal and renal function, and urine sodium loss—need to be shown. In the absence of diuretic therapy or abnormal adrenal or renal function the urine sodium concentration provides a good indicator of the state of the intravascular volume since it is mediated through the volume sensitive renin-aldosterone axis, especially as the clinical features, such as blood pressure, may be maintained despite considerable fluid depletion.

Data on urinary sodium excretion are not available in the cases presented so it is difficult to conclude whether the ADH secretion was appropriate or not in relation to the intravascular volume. For example, in case 2 many features suggest a state of fluid overload rather than depletion. These are: (*a*) the reduced concentration of serum urea (despite malnutrition, the catabolic response to trauma will increase urea production); (*b*) previous postoperative intravenous fluid treatment in the presence of postoperative stress driven ADH secretion; and (*c*) some improvement in the serum osmolality after fluid restriction. In addition hyponatraemia of such severity is more commonly seen in states of water overload than saline depletion. The evidence in this case suggests the ADH secretion to be that normally seen postoperatively rather than due to hypovolaemia secondary to hypoalbuminaemia. The excellent response to albumin infusion may have been coincidental with the decrease in stress driven ADH secretion.

Infusion of a solution containing protein into a patient who is not hypovolaemic can be detrimental, as can fluid restriction in a patient who is. Measurement of the urinary sodium concentration in addition to osmolality in hyponatraemia is necessary for accurate diagnosis and the avoidance of unnecessary and possibly dangerous treatment. The association described by Dr Dandona and his colleagues is interesting, but careful consideration of all the data are required before treatments of this kind are embarked on.

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1 Bartter FC, Schwartz WB. The syndrome of inappropriate secretion of anti-diuretic hormone. *Am J Med* 1967;42:790-806.

SIR,—On reading the interesting article by Dr P Dandona and his colleagues (2 November, p 1253) we looked at the 237 admissions into a 19 bedded acute geriatric ward and a nine bedded orthopaedic geriatric rehabilitation ward over six months to find the incidence of hypoalbuminaemia and hyponatraemia in the sick elderly.

The patients admitted had a mean (SD) age of 81·1 (9·7) years; 38 (16%) had hypoalbuminaemia (serum albumin 32 g/l), 33 (14%) had hyponatraemia (sodium 130 mmol (mEq)/l), and 15 (6%) had both. All these 15 patients had multiple diseases and seven also had had a recent operation for fractured neck of femur.

None of these patients were given infusions of plasma or albumin, although four of those with fractured femurs were given supplementary tube feeding.[1] Fourteen of the 15 patients recovered from their acute illnesses and were discharged home with improvements in their plasma albumin and sodium values. One of the 15 patients developed bronchopneumonia and pressure sores and died from these complications. Of the 23 patients with hypoalbuminaemia alone, three had values below 25 g/l but normal plasma sodium values.

These figures suggest that both hypoalbuminaemia and hyponatraemia, alone and in combination, occur commonly in the ill elderly. The cause of low plasma albumin concentrations is probably multifactorial, the major factors being increased protein turnover,[2] decreased synthesis,[3] and poor intake during illness. The causes of hyponatraemia are also likely to be multifactorial and include inappropriate antidiuretic hormone secretion due to illness, high loss of sodium via the kidney,[4] poor intake, and use of diuretics in patients with congestive cardiac failure.

While accepting that hypoalbuminaemia can lead to hyponatraemia we would suggest that in most ill elderly patients these two biochemical abnormalities are not related and probably occur as a result of illness. Treatment in these patients is not an expensive infusion of plasma or albumin but treatment of the underlying conditions and the correction of any other factor known to be responsible for the low sodium value.

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1 Bastow MD, Rawlings J, Allison SP. Benefits of supplementary tube feeding after fractured neck of femur: a randomised controlled trial. *Br Med J* 1983;287:1589-92.
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SIR,—The retrospective study of Dr P Dandona and his colleagues of six patients with hypoalbuminaemia and hyponatraemia aimed at defining a new cause of hyponatraemia—a putative syndrome of hypoalbuminaemic hyponatraemia. This is neither proved nor helpful in understanding the management of such patients who are hypovolaemic.

All six patients were probably dehydrated with low plasma volumes (the only central venous pressure quoted was 2 cm H_2O). A low plasma volume leads to an appropriate rise in antidiuretic hormone secretion[1] as shown by quoted abnormalities of urinary and plasma osmolalities. It is appropriate in the context of a low plasma volume,[2] and this overrides the action of osmoreceptors in inhibiting antidiuretic hormone secretion. To suggest that hypoalbuminaemia is a "new cause of hyponatraemia" ignores the above.

The study highlights the importance of (*a*) recognising hypovolaemia and (*b*) correcting it in the presence of hypoalbuminaemia with infusion of albumin or plasma. Crystalloid is known to remain in the circulation only 90 minutes,[3] being rapidly distributed to the extravascular space, whereas protein infusions remain intravascularly for longer—long enough after plasma and albumin, as in these cases, to switch off the stimulus to antidiuretic hormone secretion. It was this restoration and maintenance of plasma volume that improved these patients. It was not a direct effect of albumin on a physiological sensor; furthermore, it is unlikely that it is physiologically possible to measure protein separately from sodium and other osmotically active particles.

The statistically significant association of hyponatraemia with hypoalbuminaemia in 50 routine tests is misleading. Hyponatraemia is a "biochemical erythrocyte sedimentation rate, an epiphenomenon[2] of illness." Patients ill in hospital may be malnourished, recovering from surgery, and hypoalbuminaemic. I agree with the authors' conclusion that "randomly collected results from